Concepts and misconceptions in oral anticoagulation

Anticoagulants like warfarin (vitamin K antagonists (VKAs)) still have their place, however, direct oral anticoagulants (DOACs) offer unlimited advantages. This was the take-home message by Prof. Jan Beyer-Westendorf, head of the Thrombosis Research Unit in the Centre for Vascular Medicine at the Carl Gustav Carus University Hospital in Dresden, Germany. He was in South Africa (SA) from 19 to 23 September 2016, as a guest of Bayer, stating categorically that he only uses VKAs when it is unavoidable.

Anticoagulation treatment has evolved rapidly; in ~5 years, newer agents have become available, with dramatically increased use, 'In 2010 - 2011, only 4.2% of patients in the GARFIELD AF registry received DOACs. By 2014 - 2015 this figure had increased to 37%.'

DOACs offer safer alternatives to warfarin, and have been shown to facilitate patient persistence with and adherence to treatment. 'Side-effects, treatment failure and bleeding all affect compliance. The one-year discontinuation rate for warfarin is in the region of 50% v. only 15% with factor Xa inhibitors such as rivaroxaban, suggesting that the DOACs are better accepted for long-term treatment by both prescribers and patients.'

An adherence study in Canada suggests rivaroxaban's once-daily dosing regimen may offer a slight advantage over twice-daily regimens. However, it demonstrated that 25 - 30% of twice-daily prescribed DOACs are taken once daily. Regardless, dosing is a challenge. In atrial fibrillation (AF) cohorts, ~20% of patients have dose reduction owing to moderate to severe renal impairment. Prescription data suggest that 35 - 50% of DOAC prescriptions indicate insufficient dosage, so a large proportion of AF patients may be undertreated.

Real-world studies are biased by patient selection, differing designs, baseline characteristics, and treatments. Prof. Beyer-Westendorf's advice was to 'Never look at effectiveness and safety alone – look rather for net clinical benefit.' Comparing DOACs is not possible in these studies. Collectively, however, they consistently help to prevent strokes in correctly-dosed patients. They have also shown consistent safety: 'Compared to real-life studies with VKAs, not a single current study has shown higher bleeding rates with DOACs.'

Dispelling misconceptions

Prof. Beyer-Westendorf debunked four myths regarding DOACs:

Misconception one: Stable VKA-treated patients will not benefit from a switch to a DOAC. 'Guidelines actively discourage switching. But is there such a thing as a stable VKA-treated patient – and is there any evidence that they can safely continue warfarin treatment? The evidence suggests otherwise. One could argue that patients with a very stable international normalised ratio (INR) (defined as a time-in-therapeutic range or TTR of at least 70%, preferably 75%) may be regarded as stable VKA patients. However, none of the phase III DOAC studies, which evaluated only carefully selected patients treated in dedicated trial units, achieved an INR-TTR of 70% with warfarin. Furthermore, data from the ORBIT-AF study from the USA indicated that only a few patients are truly stable on warfarin and a past record of stability only weakly predicts future results'

Misconception two: With renal impairment, VKAs should be preferred. However, post hoc and meta-analyses of phase-III DOAC trials showed DOACs being as effective and safe, and in the case of factor Xa inhibitors, superior to VKAs. 'While not all thromboembolic events can be prevented, one out of five clots that would have developed with warfarin in renally impaired patients will not occur if a DOAC is used. Using a DOAC can also prevent bleeding. Pooled EINSTEIN deep vein thrombosis and pulmonary embolism data showed a 4-fold increase in major bleeding with warfarin, but not with rivaroxaban.'

Misconception three: DOACs cause more gastrointestinal (GI) bleeding than VKAs. This perception was propagated by a meta-analysis in 2013.[1] Prof. Beyer-Westendorflamented it as 'poor science', leading to gross overestimation of DOAC-related GI bleeding.[2] A subsequent study debunked this.[3] Furthermore, in GI bleeding the focus on bleeding rates may be misleading because the GI bleeding site, management and outcome need to be considered. Aspirin and VKA bleeds usually occur in the upper GI tract, while most DOAC bleeds occur in the lower GI tract. Most lower GI bleeds are haemorrhoid bleeds, which are easily managed compared with gastric ulcer bleeds. The mortality of different types of GI bleeding varies significantly and data indicate that DOACs may offer advantages in GI bleeding.

Misconception four: Managing major bleeding is simpler and better for VKAs v. DOACs. The DOAC AF studies showed the opposite. VKA major bleeding is associated with increased mortality, with worse patients experiencing less bleeding on DOACs. Prothrombin complex concentrate is praised in VKA treatment, but is often ineffective in obese patients, dosed incorrectly, and associated with thromboembolic complications. It's needed less often in DOAC patients, where it is effective. Regardless, the new agents have, or will soon have reversal options: idarucizumab for dabigatran reversal, while andexanet alfa, with anti-factor Xa activity, is an excellent alternative for rivaroxaban, apixaban and edoxaban patients. Both antidotes have yet to be registered in SA.

Prof. Beyer-Westendorf recapitulated: In real-world settings, compared with warfarin, the DOACs are associated with high persistence and adherence, as well as acceptably low stroke and major bleeding rates. VKA-associated major bleeding rates are much higher than in DOAC cohorts but since we cannot prevent major bleeding in every patient, the survival benefit in cases of major bleeding with DOACs is the main advantage over VKAs.

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3. Caldeira D, Barra M, Ferreira A, et al. Systematic review with meta-analysis: The risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants. Aliment Pharmacol Ther 2015;42(11-12):1239-1249. https://doi.org/10.1111/apt.13412

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